

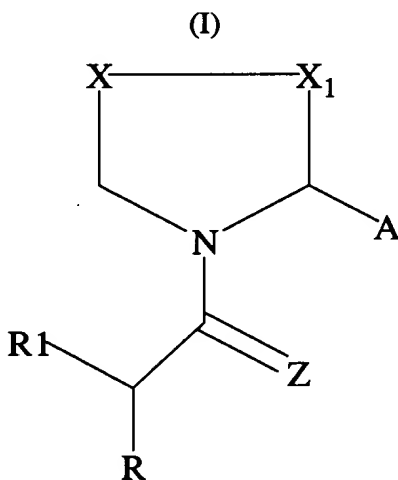
WE CLAIM:

1. An inhibitor of dipeptidyl peptidase IV, wherein the inhibitor comprises a proline mimetic and possesses an IC_{50} of no more than $1 \mu m$ and has a molecular weight of no more than 500.

2. The inhibitor according to claim 1, wherein the IC_{50} is no more than 100 nm.

3. The inhibitor according to claim 1, wherein the inhibitor can be used to treat a central nervous system disorder selected from the group consisting of strokes, tumors, ischemia, Parkinson's disease, amyotrophic lateral sclerosis and migraines.

4. A reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR₂R₃, O, S, or NR₄; with the proviso that if X is S, or if X and X₁ are both CH₂, and Z is O, and A is CN, and R₁ is H, then R is not NH substituted with C₁-C₉ straight or branched chain alkyl, or NH substituted with C₃-C₇ cycloalkyl;

X₁ is CR₂R₃, O, S, or NR₄ with the proviso that X and X₁ cannot both be a heteroatom, and with the proviso that if X and X₁ are both CH₂, and Z is O, and R₁ is NH₂, then R is not 1-methylpropyl if A is COOH, and R is not cyclopentyl if A is CN;

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO₃H, CONOH, PO₃R⁵R⁶, SO₂NHR⁷, tetrazole, amides, esters, and acid anhydrides, with the proviso that if A is CN, and R¹ is NH₂, and Z is O, and R is 1-methylpropyl, then X and X¹ are not both CH₂; X and X¹ are not S; and X is not O;

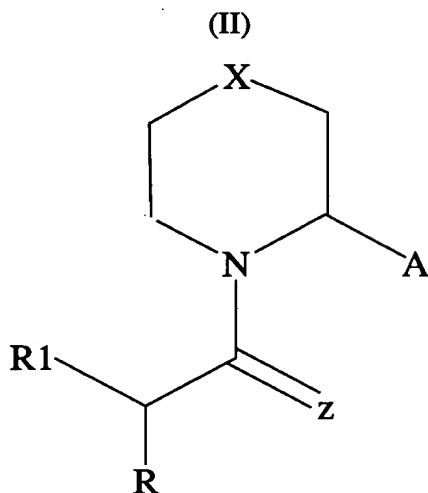
Z is O or S;

R and R¹ are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R¹ can be the same or different; and

R², R³, R⁴, R⁵, R⁶ and R⁷, if present, are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R², R³, R⁴, R⁵, R⁶ and R⁷, if present, can be the same or different.

5. The reversible inhibitor according to claim 4, wherein the inhibitor possesses an IC₅₀ of no more than 1 μm and has a molecular weight of no more than 500.

6. A reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR₂R₃, O, S, or NR₄;

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO₃H, CONOH, PO₃R₅R₆, SO₂NHR₇, tetrazole, amides, esters, and acid anhydrides;

Z is O or S;

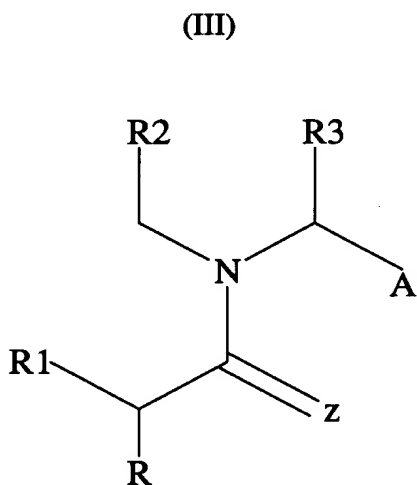
R and R₁ are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R₁ can be the same or different; and

R₂, R₃, R₄, R₅, R₆ and R₇, if present, are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol,

trifluoromethyl, or hydroxy, wherein each of R2, R3, R4, R5, R6 and R7, if present, can be the same or different.

7. The reversible inhibitor according to claim 6, wherein the inhibitor possesses an IC_{50} of no more than 1 μ m and has a molecular weight of no more than 500.

8. A reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO₃H, CONOH, PO₃R₅R₆, SO₂NHR₇, tetrazole, amides, esters, and acid anhydrides;

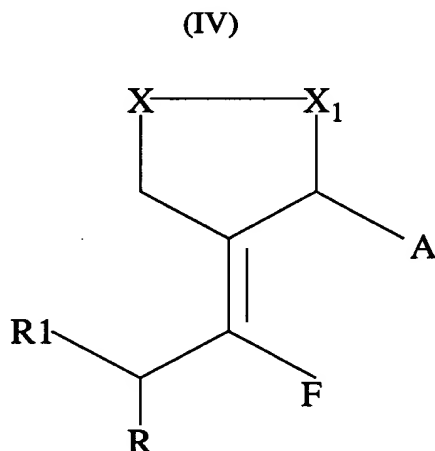
Z is O or S;

R, R1, R2 and R3 are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R, R1, R2 and R3 can be the same or different; and

R4, R5, R6 and R7, if present, are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R4, R5, R6 and R7, if present, can be the same or different.

9. The reversible inhibitor according to claim 8, wherein the inhibitor possesses an IC₅₀ of no more than 1 μ m and has a molecular weight of no more than 500.

10. A reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR₂R₃, O, S, or NR₄;

X₁ is CR₂R₃, O, S, or NR₄ with the proviso that X and X₁ cannot both be a heteroatom;

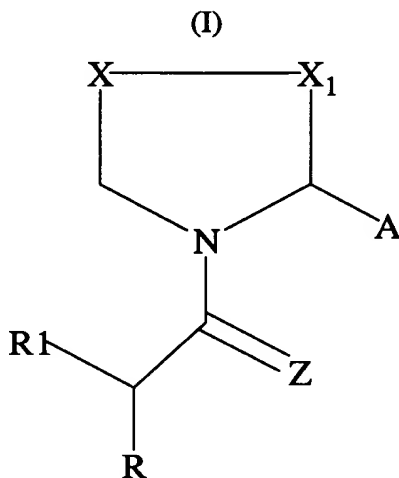
A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO₃H, CONOH, PO₃R₅R₆, SO₂NHR₇, tetrazole, amides, esters, and acid anhydrides;

R and R₁ are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R₁ can be the same or different; and

R₂, R₃, R₄, R₅, R₆ and R₇, if present, are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R₂, R₃, R₄, R₅, R₆ and R₇, if present, can be the same or different.

11. The reversible inhibitor according to claim 10, wherein the inhibitor possesses an IC₅₀ of no more than 1 μ m and has a molecular weight of no more than 500.

12. A method of treating a patient having a disorder of the central nervous system, comprising administering to the patient a therapeutically effective amount of a reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR₂R₃, O, S, or NR₄;

X₁ is CR₂R₃, O, S, or NR₄ with the proviso that X and X₁ cannot both be a heteroatom;

A is H, COOH, or isosteres of carboxylic acids, such as, one selected from the group consisting of CN, SO₃H, CONOH, PO₃R₅R₆, SO₂NHR₇, tetrazole, amides, esters, and acid anhydrides;

Z is O or S;

R and R₁ are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R₁ can be the same or different; and

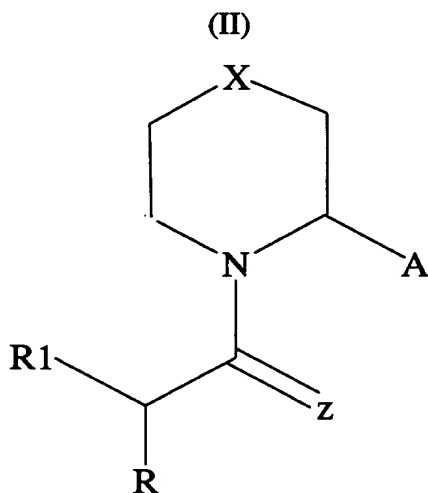
R₂, R₃, R₄, R₅, R₆ and R₇, if present, are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-

C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R₂, R₃, R₄, R₅, R₆ and R₇, if present, can be the same or different.

13. The method according to claim 12, wherein the inhibitor possesses an IC₅₀ of no more than 1 μ m and has a molecular weight of no more than 500.

14. The method according to claim 12, wherein if X is S, or if X and X1 are both CH₂, and Z is O, and A is CN, and R1 is H, then R is not NH substituted with C1-C9 straight or branched chain alkyl, or NH substituted with C3-C7 cycloalkyl; and if X and X1 are both CH₂, and Z is O, and R1 is NH₂, then R is not 1-methylpropyl if A is COOH, and R is not cyclopentyl if A is CN; and if A is CN, and R1 is NH₂, and Z is O, and R is 1-methylpropyl, then X and X1 are not both CH₂; X and X1 are not S; and X is not O;

15. A method of treating a patient having a disorder of the central nervous system, comprising administering to the patient a therapeutically effective amount of a reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR₂R₃, O, S, or NR₄;

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO₃H, CONOH, PO₃R₅R₆, SO₂NHR₇, tetrazole, amides, esters, and acid anhydrides;

Z is O or S;

R and R₁ are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R₁ can be the same or different; and

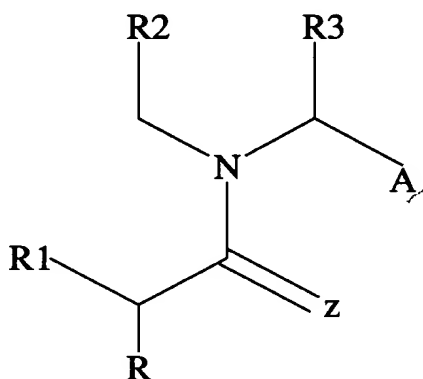
R₂, R₃, R₄, R₅, R₆ and R₇, if present, are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy,

C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R₂, R₃, R₄, R₅, R₆ and R₇, if present, can be the same or different.

16. The method according to claim 15, wherein the inhibitor possesses an IC₅₀ of no more than 1 μ m and has a molecular weight of no more than 500.

17. A method of treating a patient having a disorder of the central nervous system, comprising administering to the patient a therapeutically effective amount of a reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:

(III)



, wherein

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO₃H, CONOH, PO₃R₅R₆, SO₂NHR₇, tetrazole, amides, esters, and acid anhydrides;

Z is O or S;

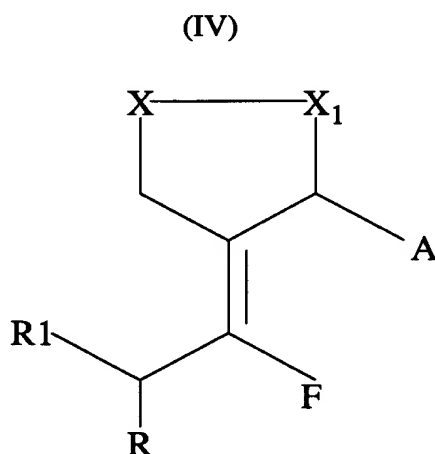
R, R₁, R₂ and R₃ are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy,

phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R, R₁, R₂ and R₃ can be the same or different; and

R₄, R₅, R₆ and R₇, if present, are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R₄, R₅, R₆ and R₇, if present, can be the same or different.

18. The method according to claim 17, wherein the inhibitor possesses an IC₅₀ of no more than 1 μ m and has a molecular weight of no more than 500.

19. A method of treating a patient having a disorder of the central nervous system, comprising administering to the patient a therapeutically effective amount of a reversible inhibitor of dipeptidyl peptidase IV, wherein the inhibitor has a core structure of:



, wherein:

X is CR₂R₃, O, S, or NR₄;

X₁ is CR₂R₃, O, S, or NR₄ with the proviso that X and X₁ cannot both be a heteroatom;

A is H, COOH, or isosteres of carboxylic acids, such as one selected from the group consisting of CN, SO₃H, CONOH, PO₃R₅R₆, SO₂NHR₇, tetrazole, amides, esters, and acid anhydrides;

R and R₁ are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R and R₁ can be the same or different; and

R₂, R₃, R₄, R₅, R₆ and R₇, if present, are independently selected from the group of functional groups consisting of H, C₁-C₉ branched or straight chain alkyl, C₂-C₉ branched or straight chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, heteroaryl and amino, wherein any of the functional groups can be substituted with one or more of C₁-C₉ straight or branched chain alkyl, aryl, heteroaryl, amino, halo, carbonyl, C₁-C₉ alkoxy, C₂-C₉ alkenyloxy, phenoxy, benzyloxy, C₃-C₈ cycloalkyl, cyano, amido, thiol, trifluoromethyl, or hydroxy, wherein each of R₂, R₃, R₄, R₅, R₆ and R₇, if present, can be the same or different.

20. The method according to claim 19, wherein the inhibitor possesses an IC₅₀ of no more than 1 μ m and has a molecular weight of no more than 500.

21. A method of treating a patient having a disorder of the central nervous system, comprising administering to the patient a therapeutically effective amount of a inhibitor of dipeptidyl peptidase IV.

22. The method according to claim 21, wherein the inhibitor comprises a proline mimetic and possesses an IC₅₀ of no more than 1 μ m and has a molecular weight of no more than 700.

23. The method according to claim 21, wherein the inhibitor has a core structure selected from the group consisting of Core Structure I, Core Structure II, Core Structure III and Core Structure IV.

24. The method according to claim 21, wherein the inhibitor is reversible.

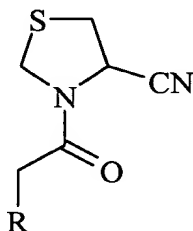
25. The method according to claim 21, wherein the central nervous system disorder is selected from the group consisting of strokes, tumors, ischemia, Parkinson's disease, amyotrophic lateral sclerosis and migraines.

26. A method of treating a patient having a disorder selected from the group consisting of strokes, tumors, ischemia, Parkinson's disease, memory loss, hearing loss, vision loss, migraines, brain injury, spinal cord injury, Alzheimer's disease, amyotrophic lateral, multiple sclerosis, diabetic neuropathy and prostate abnormalities, wherein the method comprises administering to the patient a therapeutically effective amount of a inhibitor of dipeptidyl peptidase IV.

27. A method according to claim 26, wherein the inhibitor comprises a proline mimetic and possesses an IC_{50} of no more than 1 μ m and has a molecular weight of no more than 700.

28. The method according to claim 26, wherein the inhibitor has a core structure selected from the group consisting of Core Structure I, Core Structure II, Core Structure III and Core Structure IV.

29. A method of using a reversible inhibitor of DPP-IV, comprising administering to a human patient suffering from a central nervous system disorder a pharmaceutically effective amount of the inhibitor, wherein the inhibitor is



wherein R is NH-R^I;

R^I is: C₁ - C₁₂ straight or branched chain alkyl;

C₃ - C₇ cycloalkyl;

CH₂-CH₂-NH-R^{II};

CH₂-CH₂-R^{III};

CH₂-CH₂-CHR^{IV}-R^{IV}; or

CH₂-CH₂-CH₂-R^V;

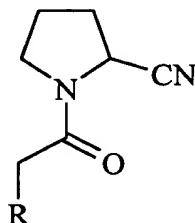
R^{II} is a pyridine ring optionally substituted in one or two positions with halo, trifluoromethyl, cyano or nitro; or a pyrimidine ring optionally substituted in one position with halo, trifluoromethyl, cyano or nitro;

R^{III} is a phenyl ring optionally substituted in one to three positions with halo or C₁ - C₃ alkoxy;

Each R^{IV} is independently a phenyl ring optionally substituted in one position with halo or C₁ - C₃ alkoxy; and

R^V is a 2-oxopyrrolidine group or a C₂ - C₄ alkoxy group.

30. A method of using a reversible inhibitor of DPP-IV, comprising administering to a human patient suffering from a central nervous system disorder a pharmaceutically effective amount of the inhibitor, wherein the inhibitor is



wherein R is NH-R^I;

R^I is: C₁ - C₁₂ straight or branched chain alkyl optionally substituted with hydroxy, acetyl, C₁ - C₃ alkoxy, or C₁ - C₃ hydroxyalkyl;

C₃ - C₁₂ cycloalkyl optionally substituted with hydroxyl, acetyl, C₁ - C₃ alkoxy, or C₁ - C₃ hydroxyalkyl;

adamantyl; indanyl; piperidyl optionally substituted with benzyl; pyrrolidine optionally substituted with benzyl; bicycloheptyl optionally substituted in one to three positions with methyl; phenyl optionally substituted with in one to three positions with halo, methoxy, trifluoromethyl; pyridyl optionally substituted in one to three positions with halo, trifluoromethyl, nitro; or pyrimidyl optionally substituted with halo, trifluoromethyl, nitro;

C₁ - C₃ straight or branched chain alkyl substituted with R^{IV}, and optionally substituted with hydroxy; or

(CH₂)₁₋₃ - NR^{II}R^{III};

R^{II} is hydrogen or methyl;

R^{III} is phenyl optionally substituted with CN, or pyridyl optionally substituted with CN; and

R^{IV} is a group selected from phenyl, naphthyl, cyclohexenyl, pyridyl, pyrimidyl, adamantyl, phenoxy, wherein the group is optionally substituted in one to two positions with ethoxy, methoxy, halo, phenylsulfide, or phenylsulfide substituted with hydroxymethyl.